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ABSTRACT

This unit is one of a group of units written to fit the Certificate of Sixth Year Studies (CSYS) chemistry course, but it could be used in most Sixth Form courses. It includes: (1) teacher notes on contents, methods, and preparation; (2) two sets of data booklets and decision sheets for two new drugs (one data booklet based on 1960 information and the other on 1980 information); (3) drug identity and background booklets for all students; and (4) a packet of seven reprints of relevant documents. Teachers distribute the two data booklets (chemical information, side effects, and points for discussion) to separate groups without any reference to dates of information; later, the teacher discloses the 20 year gap in the two sets of data. The teacher's role in promoting class discussion is of great importance, and the activity is designed to give students a clear understanding of the fact that decisions of the chemical industry are multidisciplinary. (DH)

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TO MARKET A DRUG

This unit is one of a group of units written to fit the Certificate of Sixth Year Studies course but could certainly find a place in most Sixth Form courses.

The series has been written by a group of teachers, college lecturers, university lecturers and industrialists.

It has been supported financially by the Education Appeal Fund of the Royal Soceity of Chemistry and the Education for the Industrial Society Group of the Scottish Curriculum Development Service and has received the approval of the Chemistry Panel of the Scottish Examination Board.

It is hoped that this will be used in an interactive way to give pupils the experience of making decisions for themselves on the basis of their chemical knowledge and the knowledge of other disciplines, so that they may truly see that the decisions of chemical industry are of necessity - multi disciplinary.

We realise that this unit will not be perfect and we would welcome helpful criticism so that later editions can be improved.

Dr. A.H. Johnstone
General Editor.

The writers of this unit were:-

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TO MARKET A DRUG? — TEACHERS' NOTES

FORMAT

A decision making exercise/discussion

TIME

One double period or two single periods. The unit can be more effective if the students are given the material to read prior to the class discussion.

CONTENTS OF PACKAGE

	Issue to	At
Green booklets and decision sheets entitled "To Market a Drug?"	½ Class	Start
Yellow booklets and decision sheets entitled "To Market a Drug?"	½ Class	Start
Blue booklets entitled "Drug Identity and Background"	All students	After discussion
"Magpie" of reprints of relevant background information	All students	At the end of 2 periods

GENERAL INFORMATION

The green data booklets and yellow data booklets contain data relating to two new drugs C.H.S.1 and C.H.S.2, the green booklets have been prepared using the information available in 1960 while the yellow booklets have been prepared using the information available in 1980 but these dates must not be revealed to the pupils initially.

The class should be split into small groups of up to three students with a minimum of two groups or individuals being necessary.

Half of the students are given green booklets and the other half yellow.

Each group/individual is instructed to take the booklet and use the information in it to decide whether or not to recommend buying the rights to manufacture either or both of the drugs. A decision sheet is also provided to make decisions easier.
Green and yellow groups/individuals should not mix at this point.

At the end of one period decisions should have been made and the class should be brought together for a teacher led discussion.

The first part of this is the filling in of a class summary sheet which each student has. This collects the decisions of all the groups/individuals in the class and gives a base for the discussion.

The decisions of the green and yellow groups/individuals should be different (there may in fact be differences within each colour) and the obvious question is why. At this point the teacher should disclose the 20 year gap between the two sets of data to give some historic perspective to the decisions and then promote discussion around this and the human factor involved in all decisions which must be taken.

After this the blue booklet, "Drug Identity and Background", should be given out to each student and, after giving time to read page 1, further discussion should be led by the teacher covering the two questions at the foot of that page.

Thereafter the rest of the booklet can be read by the students and the "Magpie" made available. The "Magpie" contains seven reprints of relevant documents.

TEACHER PREPARATION

The teacher's role in promoting class discussion is of great importance.

It is hoped that the seven reprints in the "Magpie", none of which is very long or involved, will provide him/her with adequate background information and that this, combined with a study of all the pupil booklets prior to their use in class, will help him/her in leading the discussion.

TO MARKET A DRUG

Data Booklet

TO MARKET A DRUG?

Two new compounds C.H.S.1 and C.H.S.2 have been synthesized by a small chemical manufacturer and tests carried out on them show that they have potential to be manufactured and marketed as new drugs.

The compounds and the results of the tests are being offered to your company (a large British pharmaceutical company) for manufacture and marketing as this is beyond the scope of the chemical manufacturer.

Your job is to consider the information contained in the following pages and, after discussing it within your group, decide whether you would recommend buying the rights to manufacture either or both of the new compounds.

Fill in the decision sheet provided as you build up your case for or against each drug.

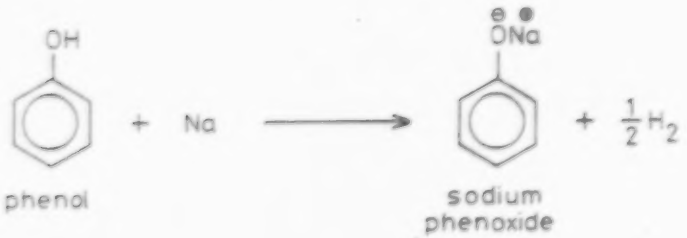
Chemical information

C.H.S.1 is a relatively simple compound which can be prepared from phenol (a plentiful supply is available from coal gas manufacture and the petroleum industry).

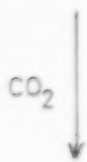
C.H.S.1 costs about 10p per 100g to manufacture which means that the product can be marketed for about 18p per 100g. (this price taking into account research and development costs, packaging, marketing, profit margins, etc.).

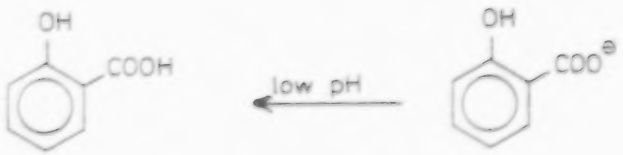
It is produced as tablets containing 300mg of the drug.

The reaction sequence is given below (only some of the chemistry will be familiar to you).

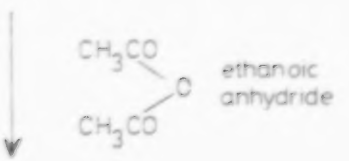


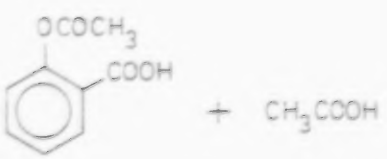
phenol — sodium phenoxide





2-hydroxybenzoic acid





2 - ethanoyloxybenzoic acid

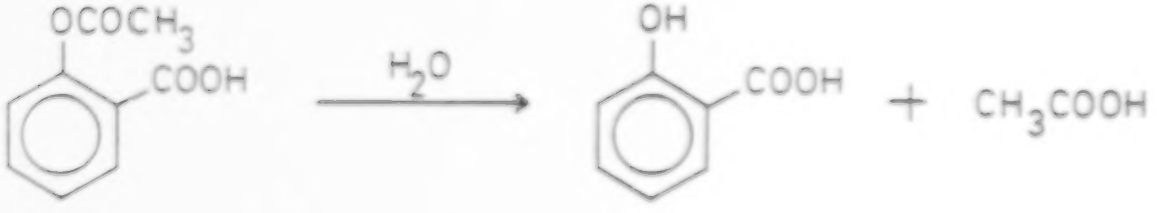
Information from Clinical Trials

C.H.S.1 has both antipyretic (fever-reducing) and analgesic (pain-relieving) effects when taken in doses of about 900-1000mg this being repeated every 3-4 hours up to a maximum of 4 doses in 24 hours.

It is recommended for so called "mild" pain, particularly toothache, headache, neuralgia, sciatica, period pains, and pains in ligaments, muscles and joints. As well as these it has a remarkable effect of reducing swelling and pain in arthritis and rheumatic fever although higher doses(up to 7g daily) may have to be administered.

Action

C.H.S.1 is stable in dry conditions for over two years. It is hydrolysed in the stomach and small intestine to give 2-hydroxybenzoic acid which passes through the stomach and intestinal wall into the bloodstream to produce its effect.



The acid itself is not administered as a drug as it has a very irritating action on the mucous membranes of the gullet and stomach making it difficult, if not impossible, to swallow.

Side Effects

When properly administered it is effective and relatively safe. It may produce stomach irritation and may cause nausea, vomiting and stomach bleeding in a few cases and therefore could aggravate stomach ulcers. Its long-term use does not lead to tolerance* or physical dependence,** and it is safe for use during pregnancy.

The toxicity of any drug is measured in terms of the weight of drug per kilogram of body weight which is required to kill 50% of a group of animals (normally rats). This is quoted as the $L.D._{50}$ (Lethal dose to kill 50%).

The $L.D._{50}$ for drug C.H.S.1 is 1750mg/kg (normal adult body weight in humans is 40-95 kg). This value makes drug C.H.S.1 safe in normal dosage.

Overdose can lead to tinnitus (ringing in the ears), dizziness, confusion and respiratory problems.

* ability of the body, after prolonged taking of the drug, to adapt to or destroy it so that it no longer carries out the job for which it was designed

** addiction to the drug

Points for discussion.

1. Do the benefits outweigh the side effects for a large proportion of the population who will have a use for the drug?
   This is expressed as the risk/benefit ratio; is this ratio good or bad?

2. Are there people who should not use the drug and therefore does this limit its usefulness?

3. Does the $L.D._{50}$ indicate that overdose would be easy or difficult?
   Does this answer give an indication of the safety of the drug?

4. What is the cost per daily dose?
   Does this seem high or low for the benefits obtained?
   This is expressed as the cost/benefit ratio; is this ratio good or bad?

   The following table may help you in reaching a decision.

Drug	Use	Approximate price per normal daily dose
Aspirin	General antipyretic analgesic substances	¾p
Soluble Aspirin		1½p
Disprin		4½p
Panadol		5½p
Paracetamol		2p

5. On the basis of your answers decide whether or not you recommend buying the manufacturing rights for C.H.S.I.

C.H.S.2.

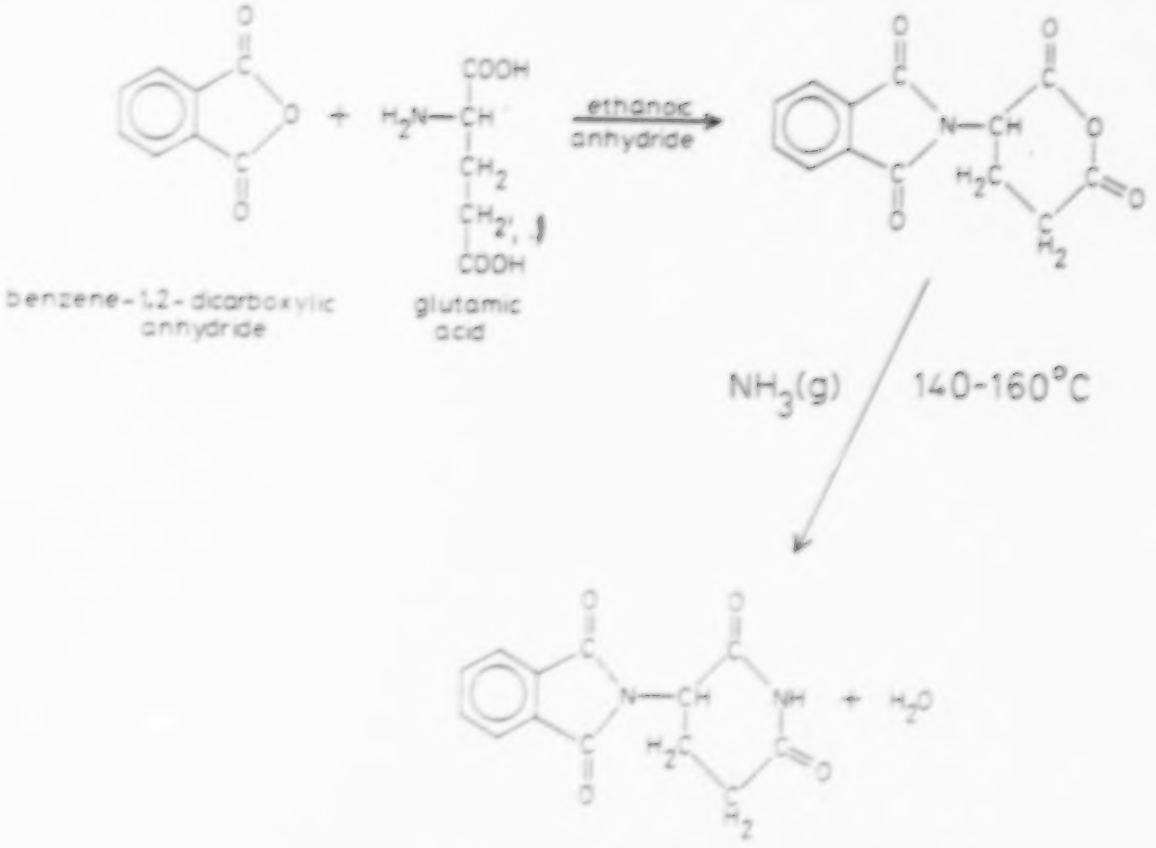
Chemical information

C.H.S.2 is a more complex compound.

It costs about £7.00 per 100g to manufacture which means a market price of £12.00 per 100g (this price taking into account research and development costs, packaging, marketing, profit margins, etc).

It is produced in tablets containing 25 or 100mg of the drug.

It is prepared according to the following reaction sequence.



2-(2,6-dioxo-3-piperidinyl)-1H-isoindole-1,3(2H)-dione

Information from Clinical Trials

C.H.S.2 is a mild sedative and hypnotic (i.e. sleep inducing) drug which is a non-barbiturate. (Barbiturates are drugs which produce a similar effect but are addictive.)

It is especially useful as a sedative during labour but can also be given to women who complain of nervousness, inability to sleep, and morning sickness associated with pregnancy. As well as these specific uses it has a more general use when mild sleep induction is required.

A common dose would be 25mg up to three times a day for sedation or a maximum of 200mg at night if used as a hypnotic (sleep inducing drug).

Action

C.H.S.2 is a stable crystalline solid. It is hydrolysed in the body giving benzene -1, 2- dicarboxylic acid, glutamic acid and ammonia.

Side Effects

When properly administered the side effects of this drug are almost nil. (Mild constipation in bed patients.) It shows no toxic effects, it does not have an addictive effect when administered over a long period of time and does not affect liver and kidneys.

It has an $L.D._{50}$ of 5000 mg/kg in rats and this makes the drug very safe, (normal adult body weight in humans is 40 - 95 kg).

Comparisons between C.H.S.2 and other sedative/hypnotic drugs are given below.

C.H.S.2	non-addictive	$L.D._{50}$	5000 mg/kg	
Luminal	addictive	$L.D._{50}$	300 mg/kg	Both widely used drugs
Valium	addictive	$L.D._{50}$	725 mg/kg	

C.H.S.2 fills the gap between the potent addictive barbiturates and the mild pain relieving sedatives like aspirin and paracetamol.

There is a growing dependence on barbiturate sleeping pills and the use of these can lead to addiction and death by overdose. C.H.S.2 will reduce this problem as it is neither addictive nor toxic in overdose.

Prolonged high dosage over a long period of time can lead to slight disturbance in the nervous system although this vanishes on reduction to normal dose levels.

Points for discussion

1. Do the benefits outweigh the side effects for a large proportion of the population who will have a use for the drug?

   This is expressed as the risk/benefit ratio; is this ratio good or bad?

2. Are there people who should not use the drug and therefore does this limit its usefulness?

3. Does the $L.D._{50}$ indicate that overdose would be very easy or difficult? Does this answer give an indication of the safety of the drug?

4. What is the cost per daily dose?

   Does this seem high or low for the benefit obtained?

   This is expressed as the cost/benefit ratio; is this ratio good or bad?

   The following table may help you in reaching a decision.

Drug	Use	Approximate price per normal daily dose
Luminal	Anti-convulsant Insomnia	½p
Valium	Sedative/tranquilliser	5p
Mogadon	Insomnia Sleep disturbances	1¾p
Debendox	Nausea Morning sickness	8¾p
Benadon	Morning sickness	4p

5. On the basis of your answers decide whether or not you recommend buying the manufacturing rights for C.H.S.2.

C.H.S.1 - DECISION SHEET

1 (a) Benefits

(b) Side effects

(c) Risk/Benefit ratio

2 (a) People to be excluded

(b) Does this limit use to a large extent?

3 Information from $L.D._{50}$

4 (a) Cost per daily dose

(b) Cost/Benefit ratio

5 Final decision

C.H.S.2 - DECISION SHEET

1 (a) Benefits

(b) Side effects

(c) Risk/Benefit ratio

2 (a) People to be excluded

(b) Does this limit use to a large extent?

3 Information from $L.D._{50}$

4 (a) Cost per daily dose

(b) Cost/Benefit ratio

5 Final decision

CLASS SUMMARY SHEET

You have now studied data relating to two drugs.

What were your decisions and the decisions of the other groups?

	GREEN				YELLOW			
	Group 1	Group 2	Group 3	Group 4	Group 1	Group 2	Group 3	Group 4
Did you/they recommend buying C.H.S.1?								
Did you/they recommend buying C.H.S.2?								

TO MARKET A DRUG

Data Booklet

TO MARKET A DRUG?

Two new compounds C.H.S.1 and C.H.S.2 have been synthesized by a small chemical manufacturer and tests carried out on them show that they have potential to be manufactured and marketed as new drugs.

The compounds and the results of the tests are being offered to your company (a large British pharmaceutical company) for manufacture and marketing as this is beyond the scope of the chemical manufacturer.

Your job is to consider the information contained in the following pages and, after discussing it within your group, decide whether you would recommend buying the rights to manufacture either or both of the new compounds.

Fill in the decision sheet provided as you build up your case for or against each drug.

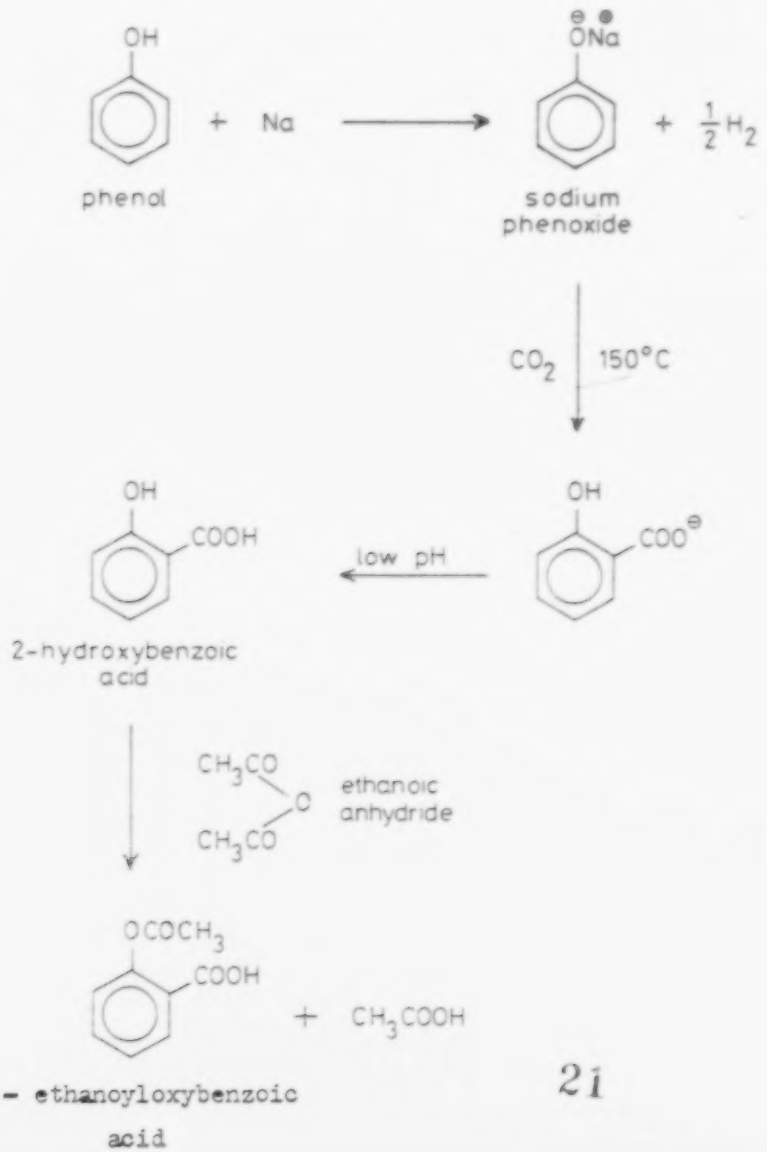
Chemical information

C.H.S.1 is a relatively simple compound which can be prepared from phenol (a plentiful supply is available from coal gas manufacture and the petroleum industry).

C.H.S.1 costs about 35p per 100g to manufacture which means the product can be marketed for about 65p per 100g (this price taking into account research and development costs, packaging, marketing, profit margins, etc.).

It is produced as tablets containing 300mg of the drug.

The reaction sequence is given below (only some of the chemistry will be familiar to you).



Information from Clinical Trials

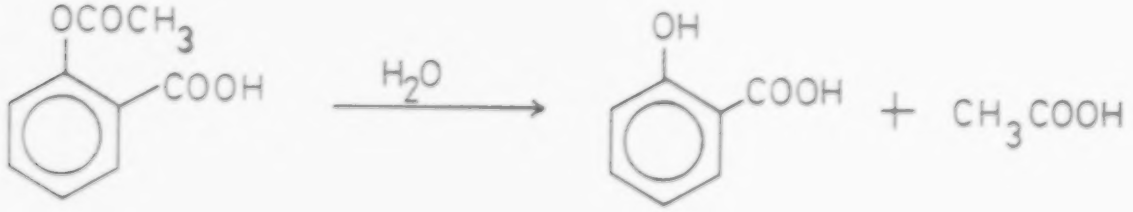
C.H.S.1 has both antipyretic (fever-reducing) and analgesic (pain relieving) effects when taken in doses of about 900-1000mg this being repeated every 3-4 hours up to a maximum of 4 doses in 24 hours.

It is recommended for so called "mild" pain, particularly toothache, headache, neuralgia, sciatica, period pains, and pains in ligaments, muscles and joints. As well as these it has a remarkable effect of reducing swelling and pain in arthritis and rheumatic fever although higher doses (up to 7g daily) may have to be administered.

In low dosage 150-300mg per day used over a long period of time C.H.S.1 can be of use in inhibiting thrombosis.

Action

C.H.S.1 is stable in dry conditions for over two years. It is hydrolysed in the stomach and small intestine to give 2-hydroxybenzoic acid which passes through the stomach and intestinal wall into the bloodstream to produce its effect.



The acid itself is not administered as a drug as it has a very irritating action on the mucous membranes of the gullet and stomach.

C.H.S.1 acts by inhibiting the synthesis of Prostaglandins (P.G.) in the body. P.G.'s are complex C_{20} cyclic carboxylic acids and are identified by letter labels, e.g. PGE, PGF, etc. P.G.'s have many functions, amongst them they produce redness and heat, swelling and pain. C.H.S.1 inhibits the enzyme induced formation of PGH_2 from which the P.G.'s, which produce the symptoms above are formed. Hence reduction in redness and heat, swelling and pain are noted after administering C.H.S.1.

As well as cutting the supply of these P.G.'s others are also inhibited, e.g. the P.G. which causes blood clotting, hence the use of C.H.S.1 in inhibiting thrombosis.

Side Effects

When properly administered it is effective and relatively safe. Its long-term use does not lead to tolerance* or physical dependence**.

The toxicity of any drug is measured in terms of the weight of drug per kilogram of body weight which is required to kill 50% of a group of animals (normally rats). This is quoted as the $L.D._{50}$ (Lethal dose to kill 50%). The $L.D._{50}$ for C.H.S.1 is 1750 mg/kg (normal adult body weight in humans is 40 - 95 kg). This value makes it safe in normal dosage.

C.H.S.1 has no effect on the central nervous system, liver or kidneys except in extreme overdose. It can produce stomach bleeding of 1.5 - 3.0 cm^3 per day but this is a very small amount and is usually unnoticed by patients (a normal person can lose this amount without taking the drug).

0.2% of the population are intolerant to the drug and up to 28% of chronic asthmatics can have a bout of asthma brought on by using the drug.

Blood disorders like anaemia can be caused in some patients, mainly by blood loss. Iron deficiency anaemia is the commonest but others are possible. These cases can however be treated by removal of the drug or in the cases where the drug is essential by the prescription of iron tablets.

There are no tumour-inducing or carcinogenic effects related to the taking of C.H.S.1.

The taking of the drug before and during early pregnancy may induce abortion and a prolonged labour and excess bleeding in mother and baby can be attributed to the drug.

* ability of the body, after prolonged taking of the drug, to adapt to or destroy it so that it no longer carries out the job for which it was designed.

** addiction to the drug

Care should also be taken in prescribing this drug to patients already taking other drugs as there may be interaction.

Overdose leads to tinnitus (ringing in the ears), dizziness, confusion and respiratory problems.

The blood clotting ability of the body is reduced by taking C.H.S.1 and this can be a drawback producing longer bleeding times, however in low dosage this can be used to advantage in the prevention of thrombosis. (See last paragraph of Action).

Points for discussion

1. Do the benefits outweigh the side effects for a large proportion of the population who will have a use for the drug?

   This is expressed as the risk/benefit ratio; is this ratio good or bad?

2. Are there people who should not use the drug and therefore does this limit its usefulness?

3. Does the $L.D._{50}$ indicate that overdose would be easy or difficult? Does this answer give an indication of the safety of the drug?

4. What is the cost per daily dose?
   Does this seem high or low for the benefits obtained?
   This is expressed as the cost/benefit ratio; is this ratio good or bad?

   The following table may help you in reaching a decision.

Drug	Use	Approximate price per normal daily dose
Aspirin)	General	2½p
Soluble Aspirin)	antipyretic	4½p
Disprin)	analgesic	13 p
Panadol)	substances	14 p
Paracetamol)		5 p

5. On the basis of your answers decide whether or not you recommend buying the manufacturing rights for C.H.S.1.

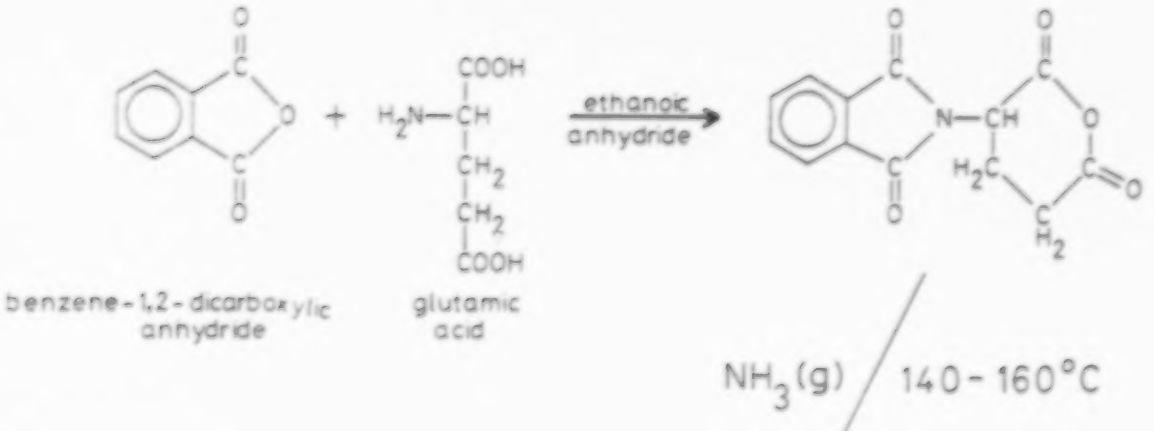
Chemical information

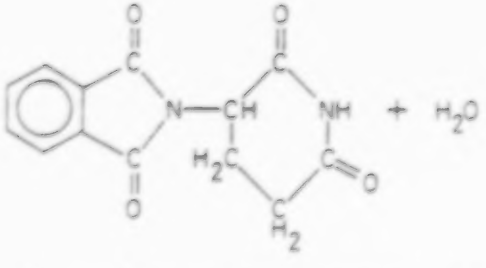
C.H.S.2 is a more complex compound.

It costs about £35.00 per 100g to manufacture which means that the product can be marketed for about £60.00 per 100g. (this price taking into account research and development costs, packaging, marketing, profit margins, etc.).

It is produced in tablets containing 25 or 100mg of the drug.

It is prepared according to the following reaction sequence.





2-(2,6-dioxo-3-piperidinyl)-1H-isoindole-1,3(2H)-dione

Information from Clinical Trials

C.H.S.2 is a mild sedative and hypnotic (i.e. sleep inducing) drug which is a non-barbiturate. (Barbiturates are drugs which produce a similar effect but are addictive.)

It is especially useful as a sedative during labour but can also be given to women who complain of nervousness, inability to sleep and morning sickness associated with pregnancy. As well as these specific uses it has a more general use when mild sleep induction is required.

A common dose would be 25mg up to three times a day for sedation or a maximum of 200mg at night if used as a hypnotic (sleep inducing drug).

Action

C.H.S.2 is a stable crystalline solid. It is hydrolysed in the body giving benzene -1,2- dicarboxylic acid, glutamic acid and ammonia.

Side Effects

It has an $L.D._{50}$ of 5000mg/kg in rats and this makes the drug very safe, (normal adult body weight in humans is 40 - 95 kg).

Comparisons between C.H.S.2 and other sedative/hypnotic drugs are given below.

C.H.S.2	non-addictive	$L.D._{50}$	5000 mg/kg	
Luminal	addictive	$L.D._{50}$	300 mg/kg	Both widely used drugs
Valium	addictive	$L.D._{50}$	725 mg/kg	

C.H.S.2 fills the gap between the potent addictive barbiturates and the mild pain relieving sedatives like aspirin and paracetamol.

Humans have differing reactions to C.H.S.2. In many there are no side effects especially when taking small doses over a short period of time. Others however suffer from one or more of the following - giddiness, nausea, shivering, constipation, symptoms similar to a "hangover" and buzzing in the ears (tinnitus). In some cases there are effects on the circulation producing coldness or "pins and needles" in hands and feet. These effects clear up on removal of the drug. At high dosage disturbance to the central nervous system can take place and trembling can be noticed. Dosage over a long period of time can lead to polyneuritis, a nervous degeneration which cannot be reversed. In pregnant women C.H.S.2 can cross the placenta and enter the embryo and because of this there is a possible teratogenic (monster making) effect if the drug is taken in the first two months of pregnancy. The drug can produce defects in eyes, ears, arms and legs.

Points for discussion

1. Do the benefits outweigh the side effects for a large proportion of the population who will have a use for the drug?
   This is expressed as the risk/benefit ratio; is this ratio good or bad?

2. Are there people who should not use the drug and therefore does this limit its usefulness?

3. Does the $L.D._{50}$ indicate that overdose would be easy or difficult?
   Does this answer give an indication of the safety of the drug?

4. What is the cost per daily dose?
   Does this seem high or low for the benefit obtained?
   This is expressed as the cost/benefit ratio; is this ratio good or bad?

   The following table may help you in reaching a decision.

Drug	Use	Approximate price per normal daily dose
Luminal	Anti-convulsant Insomnia	2p
Valium	Sedative/tranquilliser	6p
Mogadon	Insomnia Morning sickness	4p
Debendox	Nausea Morning sickness	20p
Benadon	Morning sickness	8p

5. On the basis of your answers decide whether or not you recommend buying the manufacturing rights for C.H.S.2.

C.H.S.1 - DECISION SHEET

1 (a) Benefits

(b) Side effects

(c) Risk/benefit ratio

2 (a) People to be excluded

(b) Does this limit use to a large extent ?

3 Information from $L.D._{50}$

4 (a) Cost per daily dose

(b) Cost/benefit ratio

5 Final decision

C.H.S.2 - DECISION SHEET

1 (a) Benefits

(b) Side effects

(c) Risk/benefit ratio

2 (a) People to be excluded

(b) Does this limit use to a large extent?

3 Information from $L.D._{50}$

4 (a) Cost per daily dose

(b) Cost/benefit ratio

5 Final decision

CLASS SUMMARY SHEET

You have now studied data relating to two drugs.

What were your decisions and the decisions of the other groups?

	GREEN				YELLOW			
	Group 1	Group 2	Group 3	Group 4	Group 1	Group 2	Group 3	Group 4
Did you/they recommend buying C.H.S.1 ?								
Did you/they recommend buying C.H.S.2 ?								

TO MARKET A DRUG

Drug identity and background

DRUG IDENTITY AND BACKGROUND

C.H.S.1 - ASPIRIN

C.H.S.2 - THALIDOMIDE

Aspirin was first prepared in 1893 and was in large scale production by 1900. It has now become the most widely used of all analgesics (pain relievers) and is widely accepted as the "cure all" despite all the now known side effects.

Thalidomide was first prepared in 1953 and marketed in 1958 as a non-barbiturate therefore non addictive sedative and hypnotic. Its principal advantage was that any overdose was not lethal. It was in 1961 that the weight of evidence suggesting that thalidomide could cause permanent nerve damage and gross deformities in babies born to mothers who had taken the drug, caused it to be removed from the market. From that date a protracted legal debate raged for many years in an attempt to gain compensation from the Distillers Company who marketed the drug in Britain; a settlement being reached in 1973 which has cost the company £30 million to date for the 400-450 children involved.

Aspirin is still the most widely used analgesic, even although it has a large number of side effects, while Thalidomide was used only for a relatively short period of time before the side effects reported were considered too serious for it to be retained on the market.

This seems enigmatic.

How were these drugs allowed to come onto the market?

How do we try to stop drugs like Thalidomide coming on to the market today?

Give these questions some thought and discuss possible solutions.

ONE ANSWER - BUT .....

In the early 1960's a Labour MP, Kenneth Robinson said "any drug manufacturer could market any product, however inadequately tested, however dangerous, without having to satisfy any independent body as to its efficacy (effectiveness) or its safety".

After the thalidomide disaster public outcry forced the government to act. They set up the Joint Sub-Committee on Safety of Drugs in 1962 under the late Lord Cohen and as a result of their report the Committee on Safety of Drugs was formed in 1964 to invite drug manufacturers to submit reports as they "may think fit" on the safety, testing and trials in humans of new medicines. This was an interim measure to allow legislation to be prepared and passed through parliament. In 1968 the Medicines Act became law and the Committee on Safety of Medicines (CSM) was set up to administer the Act. Under the Act drug companies can only market new medicines under licence and to gain a licence they must submit to the CSM information about, amongst other things, the toxicity, teratology (monster making effect), metabolism and carcinogenic effects of the proposed new medicine. A simple application form MLA 201 (attached) must be filled in and presented along with details described in MLA 201 Parts 1A and 1B (attached) and MLA 201 Part II which asks questions about description of product, manufacturer and quality control, development of the drug, stability, metabolism (how the body breaks the drug down and uses it), studies in animals including reproduction studies and carcinogenic effects, human trials and adverse reactions. MLA 201 Part II is a 40 page document !!..... therefore the information required is vast.

Medicines and drugs marketed prior to 1968 (eg. aspirin) were given licences and these were to be reviewed as soon as possible. Aspirin was reviewed in 1978.

There is also a continuous monitoring of side effects via G.P.s. They send reports of any adverse reactions to any medicine or drug to the CSM where they are collated and a few products have had licences withdrawn on this evidence.

The system is not foolproof and it has its critics.

Animals tests do not mean that the drug will be safe in humans. Tests on rats are cheaper than tests on monkeys but results on monkeys are often more reliable when projected into humans. Animal tests however, give a good indication of any serious toxic reactions.

Some side effects only become apparent after prolonged taking of the drug and this is where G.P.'s adverse reactions report is of vital importance. Is it reasonable to put this responsibility on a G.P. or should clinical trials be longer? Some say it is not a G.P.'s responsibility and therefore clinical trials must be longer.

All testing and trials cost money and a company gets no return on its investment until the new drug is marketed so companies are not in favour of prolonging testing and trials. They feel that it can be done more than adequately in terms of the 1968 Act and its proposed revisions of 1981 which ease the regulations slightly.

It should now be obvious to you that decision making in this area is not easy, facts and figures can be manipulated and different results can come from the same set of data.

Nobody has the perfect answer, but you, as this country's future chemists, pharmacists, doctors, dentists, engineers, accountants, M.P.s, consumers, etc. will have some say, however small, in making decisions like these.

The "Magpie" contains the following reprints which give interesting background to the discussion you have had.

1. How we keep unsafe drugs off the market - New Scientist 4.12.1980

2. How a new drug reaches the market - New Scientist 4.12.1980

3. Watching for side-effects - New Scientist 4.12.1980 and CSM

4. Is safety too expensive? - Sunday Times 5.4.81

5. Analgesics - Is the 50 year search finally over? - Chemistry in Britain 17 (6) 1981

6. A market for pharmaceuticals - Education in Chemistry 15 (4) 1978

For people who are interested in further reading the following books can be consulted -

1. Suffer the Children - The Sunday Times Insight Team - Andre Deutsch

2. Chemistry and the Needs of Society - The Chemical Society Special Publication No 26

3. Chemistry in Industry, Food and Drugs - Peter Tooley - John Murray

4. The development of new drugs - Science in Society Project, Heinemann/ASE.

PART I - Application Form

Form MLA 201 obtainable from Medicines Division should be used for this part

MEDICINES ACTS 1968 and 1971 - APPLICATION FOR PRODUCT LICENCE

1. Name of Product: If the marketing name is not yet settled, give another (possibly temporary) name by which the product can be identified.

2. (i) Full name and address of proposed licence holder:

The licence could be held by individuals or by legal persons such as Limited Companies. In the latter case the company's full legal style, registration number and registered address should be stated here. If some other title (eg a division of the company) is to be shown on the licence it should be shown against trading style

(ii) Address for correspondence if different from above:

3. Trading style to be shown on licence if different from above:

4. Role of proposed licence holder: (See paragraph 3.3 of the Guide to the Licensing System - MAL 1).

(i) as person responsible for composition of product manufactured in UK.
(ii) as person who imports or procures its importation.
(iii) as person who first sells or supplied it as a medicinal product.

5. Activities for which licence is required:

(i) selling or supplying product in the UK.
(ii) procuring the manufacture or assembly of the product for sale or supply in the UK.
(iii) importing or procuring the importation of the product.

Delete amend or add as necessary

(iv)

6. Applicant's own reference no:

7. Details of earlier applications: (ie under Medicines Act or earlier voluntary scheme, successful or not) - give reference number -

8. To cover sale and supply of the product manufactured before the grant of the licences: YES/NO

9. Scientific Evidence:

(i) Chemistry and Pharmacy Pages
(ii) Experimental and Biological Studies Pages
(iii) Clinical Trials Pages

Insert number of pages in each part.

10. Number of pages of product particulars - Part IA

Give numbers of pages in Part IA

11. I/we apply for the grant of a product licence to the proposed holder named above in respect of the Product s to which the Product Particulars on Page 2 refer and in accordance with the other particulars annexed: the said licence to be for a period of five years and subject to the following provisions-

11.1. All the Standard Provisions applicable to product licences under regulations for the time being in force under Section 47 of The Medicines Act 1968.

11.2. The product shall not be recommended to be used for any purpose other than those specified in the Product Particulars as Uses and shall be sold or supplied in accordance with the said Product Particulars except in so far as may from time to time be approved by the Licensing Authority.

11.3. The specification of the constituents and of the finished product shall be in accordance with the information contained in or furnished in connection with the application.

11.4. The product is to be manufactured only in accordance with the methods set out in this application or furnished in connection with it.

11.5. No material information has been omitted (within the knowledge of the signatory).

Date .....

Signature .....

State capacity in which signed

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Product Particulars

1. Name of Product:

   If the marketing name is not settled this should be left blank and the name notified later as available.

2. Pharmaceutical form:

   Describe the pharmaceutical form eg tablets, capsules, injections, and state whether the product is (a) in a form for administration to human beings: or (b) for use as an ingredient in preparing medicinal products.

3. Active constituents:

   Indicate the way in which the active ingredients and quantities will be declared on any leaflet, label or descriptive material. Each constituent should be described under (a) its approved name or monograph name: or (b) where there is no approved name or monograph name the non-proprietary designation or other descriptive appellation by which it can be readily identified: or (c) the trade name in other cases.

4. Uses:

   State recommended clinical use the proposed route(s) of administration and any directions for use to be included in labels and leaflets.

5. Recommended dose and dosage schedule:

   State the recommended dosage for:
   (i) adults and if appropriate (ii) children and infants by age groups. Where appropriate, distinguish between therapeutic and prophylactic doses and between dosages recommended for different clinical uses.

6. Contraindications, Precautions and Warnings:

   State particulars of contraindications, warnings and precautions to be included in the data sheet, container label, package label or any leaflets.

7. Method of retail sale or supply:

   State whether it is proposed to make the product available:
   (a) for general sale: or (b) only through registered pharmacies - (i) for over the counter sale: or (ii) as a prescription item or (c) through some other specified group of outlets eg hospitals, specialised clinics laboratories from automatic machines or herbal practitioners

8. Manufacturer of dosage form:

   State the name(s) and address(es) of the manufacturer(s) of the dosage form.

Applicants reference number (as on page 1)

Applicants signature.....

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PART IB SUPPLEMENTARY DETAILS

1. PRODUCT LITERATURE

1.1	Labelling and package inserts	Details of the proposed labelling and package inserts.	
1.2	Data sheets	The text of any data sheet should be given, if appropriate.	This can be supplied at a later stage if it is intended to defer final drafting until the licence is granted. Applicants should check that ALL labelling complies with the provisions of the Medicines (Labelling) Regulations 1976 (SI No. 1726) and data sheets comply with the provisions of the Medicines (Data Sheet) Regulations 1972. The Department issues guides to these regulations which are available on request: MAL 25 Notes on Data Sheets. MAL 42 Notes on the Medicines (Labelling) Regulations 1976.

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2. BACKGROUND

2.1	Applications in other countries	If authorisation to market this product has been granted, by the appropriate regulatory authority in any other country, give the country, date and outcome.	Any explanatory details that you consider relevant may also be given, including reasons for revocation or refusal of marketing authorisation in another country.
2.2	Background	Any other historical or background information which may assist in the assessment of the application should be given here.	For new drug applications it is often helpful to indicate whether the substance has been newly developed or whether the early development work was carried out some years back, since the techniques used may in some instances appear outmoded.

3. PERSONS INVOLVED IN THE MANUFACTURE OF THE FINISHED PRODUCTS AND THEIR DISTRIBUTION IN THE UK

3.1	Manufacturer(s) and Assembler(s)	The name and address of each place at which each stage of the manufacture and assembly takes place indicating briefly the manufacturing or assembly operations involved. For UK companies give the manufacturer's licence number for each company.	
3.2	Arrangements for storage	The arrangements made for storage of the product by the proposed licensee or on his behalf and the address of each place of such storage.	Only a brief outline of the storage arrangements is required.
3.3	Importer	The name and address of the actual importer if this is other than the licence holder.	
3.4	Responsibility for quality control	State: (a) whether the licence holder will be responsible for deciding if any batch of the product is acceptable for release for marketing; if not, who will be responsible. (b) Where the quality control will be carried out.	

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TO MARKET A DRUG

Magpie

How we keep unsafe drugs off the market

Ten years ago saw the creation of Britain's first statutory system for improving the safety of drugs. Sir Eric Scowen ran that system until he retired this year—*New Scientist* interviewed him to find out if things have improved since the thalidomide scandal

Frank Lesser is a freelance writer on drugs and an ex-lecturer in pharmacology

The Committee on Safety of Medicines (CSM) is 10 years old. It was born in the wake of the thalidomide disaster and is the most important part of the machinery that the Medicines Act of 1968 set up to regulate the introduction of new medicines in Britain. The pharmaceutical industry continually attacks the testing the committee demands as unnecessarily restrictive. And the press seizes upon occasional reports of damage induced by drugs as evidence of the committee's failings. But how well has the CSM really worked?

Sir Eric Scowen

The Medicines Act was a direct consequence of the thalidomide disaster. At that time, as the Labour MP Kenneth Robinson said, "any drug manufacturer could market any product, however inadequately tested, however dangerous, without having to satisfy any independent body as to its efficacy [effectiveness] or its safety". The Joint Sub-Committee on Safety of Drugs, which the government set up in 1962 under the chairmanship of the late Lord Cohen of Birkenhead, reported that there was "a specially urgent need to take whatever steps were immediately possible to improve the safety testing of drugs". As a result of the sub-committee's report, the government created the Committee on Safety of Drugs—commonly known as the Dunlop committee after its chairman. On 1 January, 1964, this committee began "to invite" drug manufacturers to submit to it reports, as they "may think fit", on the safety testing and trials in humans of new medicines.

Even more revolutionary than this was the joint sub-committee's insistence "that legislation on the whole subject is urgently required. No interim measures should be regarded as justification for delaying this essential task" because any arrangements "would obviously be more effective with legislative sanction than without".

That is the view too, of Sir Eric Scowen, the first chairman of the CSM who retired this year and is now chairman of the Imperial Cancer Research Fund. It was the constant endeavour of the new CSM, he said, to continue the informal approach the Dunlop committee developed under the voluntary arrangements it operated. But the 1968 Act meant that drug companies could market new medicines only under licence. And, in order to gain a licence, companies were obliged by the law to submit to the CSM information about the quality, the toxic effects and effectiveness (efficacy) of new medicines.

The experience of the Dunlop committee underlined the need for a statutory basis for regulating new drugs. Thus, in its annual report for 1966, the Dunlop committee reported that "203 applications were made for the release of drugs for clinical trials. Frequently these applications were made at a time when tests for the effects of the drugs on pregnant animals had not been undertaken." While the committee accepted that tests in animals to discover whether drugs damaged the unborn fetus were far from perfect, it proclaimed that; "only in the most exceptional circumstances will the committee release any drug for clinical trial in women of child-bearing age until the appropriate tests on animals have been carried out satisfactorily". That the committee found it necessary to repeat this warning in its next annual report proves that some drug manufacturers had found the harsh experience of thalidomide not difficult to forget. "In the CSD days," Scowen commented, "we were fighting the early battles. We still occasionally have to fight the battle; but it is now generally accepted that if a drug is to be used in women of child-bearing age, full teratogenicity testing . . . ought to be done."

However, the change from voluntary to statutory controls has not altered the nature of the essential problem of new drugs. In a word, most—if not all—experts on drugs would say that there is not, and cannot be, such a thing as a *safe* drug. Any effective drug is bound to have effects on the body other than the intended ones. The best scientists can achieve is to limit this damage, first, by ensuring that drugs are tested adequately before giving them to patients; secondly, by clinical trials on a limited number of patients; and thirdly, by setting up a system of surveillance once the drug is generally available to watch for any ill-effects that were not seen in testing.

The drug industry has frequently criticised the testing for toxicity and efficacy in both laboratory animals and human volunteers that the CSM demands before granting a certificate allowing clinical trials to go ahead. It often claims that animal experiments can only suggest—and not predict—what may happen in man. On the other hand, Professor G. Zbinden of Zurich University, director of the Swiss Institute of Toxicology, said at the World Conference on Clinical Pharmacology and Therapeutics in London this summer that; "a large number of serious toxic reactions of potential new drugs can be detected reliably with toxicological tests. To deny the scientific basis and validity of experimental toxicology," he went on, "is an irresponsible act that could hurt the development of essential new drugs and could cause serious harm to mankind."

It is easy to rail against the pre-clinical testing that CSM requires drug companies to perform, complaining about the waste of time, money and scientific manpower involved. But when Scowen challenged the companies to say which of the tests the committee requires are unnecessary, they returned no answer. Furthermore, Scowen insists, the CSM is always ready to consider evidence that particular tests are of no value, and the Department of Health and Social Security currently has before it proposals, from a working party under Professor D. G. Grahame-Smith of Oxford, to modify the guidelines in which the CSM lays down the tests drug companies must perform.

It is also worth pointing out that, on the basis of 12 years' experience with the Medicines Act, industry is in a position to mount an all-out assault on the pre-clinical testing requirements—if the facts warranted such an attack. But the CSM, on the other hand, cannot—by law—defend itself by publishing the information companies have submitted to it in support of applications for licences. That industry has not mounted such an assault may reflect its awareness that the present circumstances suit it very well.

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By meeting the CSM's requirements, industry may say that it has done everything possible. At the same time, it can lay the blame for the escalating cost of developing new medicines—and their relative rarity—at the door of the regulatory agency.

On this last point—that regulation has inhibited the introduction of new drugs—Scowen said he has no evidence to justify the charge that the controls CSM has implemented have reduced the number of new drug *substances* submitted to the committee. Most of the submissions it receives, in fact, relate to new formulations of existing medicines; yet industry's complaints about the cost and time involved in introducing new drugs relate only to new drug substances. New formulations are considerably cheaper to develop.

Once a company has reported its clinical trial to the CSM and the committee has recommended that a licence be granted, the company can market the drug. At this stage, the CSM has the task of "promoting the collection and investigation of information relating to adverse reactions" —that is, noting any ill-effects the drug may have on patients. Fortunately, there has been only one serious case of adverse reactions to a new medicine since CSM came into existence—involving practolol (Eraldin). ICI marketed practolol in 1970 for treating disturbances of heart rhythm. The drug had passed through its pre-clinical and clinical testing stages under the old Dunlop committee and therefore received a licence of right under the Medicines Act.

Within two years of being marketed, according to some medical practitioners, ICI knew that some patients taking practolol had suffered severe skin reactions, which subsided when they stopped taking the drug and recurred when they started taking it again. Between June and December, 1974, reports in the medical press confirmed this toxic effect, as well as noting others involving eye disorders and a thickening of the membrane lining the abdominal cavity (sclerosing peritonitis), which obstructed the intestine.

In July and October, 1974, ICI warned physicians and pharmacists that any patient receiving Eraldin and suffering from skin and eye disorders should have the drug withdrawn immediately. In January 1975, CSM issued a formal warning of the drug's side-effects to physicians. So well established were these toxic reactions that in 1975 the New Zealand Department of Health issued a letter to medical practitioners stating that, from 1 March, 1975, ICI would withdraw supplies of Eraldin (except to hospitals) "because of continuing reports in New Zealand and from other countries of severe reactions involving the cornea, skin, pericardium and peritoneum, not all of which are reversible". In Britain, ICI sent a third circular in April 1975, warning particularly against the danger of sclerosing peritonitis. Only in July and—as parliament was later told —after consultations with CSM, was the action taken in New Zealand duplicated here in the form of a letter from ICI warning that it would supply only hospitals.

The CSM's failure to take the initiative raised doubts about its *surveillance of* drugs *after* their introduction and produced a resurgence of the demand, first heard after the thalidomide disaster, for urgent action to ensure that adverse reactions to new drugs should be spotted and reported as quickly as possible.

In February, 1978, the CSM began consulting interested parties about its proposed Recorded Release Scheme (RRS) and an associated pilot study of one selected drug. In this proposed scheme, CSM would identify patients taking a drug and follow their clinical progress, watching for any unexpected events as well as clear-cut adverse reactions. There were objections to this scheme from various sources, and so the CSM proposed a modified system called Retrospective Analysis of Drug Safety (RADS—see box) and another scheme for linking the medical records of hospital patients with their "drug history".

Despite the need for urgent action, nothing has been done to improve surveillance of the side-effects of new drugs. The Minister for Health told the House of Commons recently that he had shelved CSM's schemes for surveillance because of "the paramount need to restrain public expediture". Thus, only drug monitoring schemes devised by the manufacturers themselves are actually in operation, despite the obvious conflict of interest involved.

Scowen's view of all this is that once a proper surveillance system began to work, it would probably cost no more to follow up six drugs than one. He also thinks some of the figures quoted by spokesmen for the drug industry for the likely cost of surveillance are wildly exaggerated. Equally, he is in no doubt that it is essential to improve the existing arrangements.

So has CSM been a success? It has certainly consolidated the regulatory work of its predecessor and established standards for the testing of new medicines that have kept some 10 per cent of the preparations submitted to it off the market. The possibility that some of them might—despite the results of animal experiments—have proved to be non-toxic in man is real. But only continuing advance in our knowledge of how drugs act can reduce that risk.

And yet, despite the Medicines Act and its regulations, CSM did little better with practolol once it had been marketed than was done without the legislation in the case of thalidomide. The urgency of measures to institute systematic surveillance to replace the CSM's present random and spontaneous collection of reports of adverse reactions can hardly be overstated. □

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How a new drug reaches the market

Drug companies put every new potential medicine through a batch of tests to determine what, if any, actions they have, and how potent they are. Promising substances then go through simple preliminary toxicity tests. If the potential drug passes these tests, the firm may decide that it has a chemical worth submitting to the Committee on Safety of Medicines to approve.

The CSM lays down the information it requires when the company submits an application for a clinical trial certificate. The CSM lays down the studies the firm must carry out in considerable detail. They concern the chemistry, pharmacy (quality), efficacy and toxicity—mainly by animal experiments in specified species—of the new substance. Most firms deciding to make a submission will also report their observations on the administration of the new medicine to healthy human volunteers.

The CSM, which meets monthly, replies either by granting a clinical trial certificate or by asking for more information. In the latter case, the firm may decide not to proceed. If the CSM decides not to grant a certificate, the firm can appeal to the Medicines Commission.

The clinical trial itself is in two stages. In the first, the patients, whose numbers must be given in the application and who must give informed consent to take part, receive the drug to determine whether the proposed dosage is likely to be effective and whether obvious ill-effects occur when patients take this dosage. It is at this stage that many companies decide not to proceed, either because the drug is less effective than they hoped, or because it is more toxic than the earlier animal experiments had indicated.

If phase I is successful, phase II—the clinical trial proper—begins, on patients suffering from the condition(s) stated in the company's application for a trial certificate. The company submits the results of the trial to the CSM as an application for a product licence, without which no medicine may be marketed. If the CSM recommends that licence be granted, the firm can go ahead and market the new medicine.

Should the CSM either require more information or refuse a licence, the company can appeal to the Medicines Commission. Last year the CSM considered 180 applications for product licences (of which, only 81 were granted), but most of these were for new formulations of medicines already on the market and so already approved. □

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Watching for side-effects

Retrospective Assessment of Drug Safety (RADS) is a scheme for monitoring the side-effects of drugs on the market that the CSM proposed to the Minister for Health. The minister estimates that the pilot study of RADS which the committee wanted to run for one new medicine could cost £500 000.

The main feature of the scheme is that it would identify and follow up all patients receiving the new medicine until sufficient time had elapsed, or numbers of patients had been observed, to absolve the drug of undue risk. This is how it would work. A new medicine appears on the market. CSM decides that it is sufficiently novel and important (because large numbers of people may need to take it for long periods) to run a RADS study on it. The first step is for CSM to alert the Prescription Pricing Authority, to which pharmacists send all NHS prescriptions for medicines for pricing and payment. The authority will then send copies of all prescriptions for the new medicine to the CSM. When the CSM has received copies of 10 000 prescriptions, it will issue a form to the doctors who prescribed the drug, asking them to record any important events in the medical history of the patients who took the drug "even though you have no reason to suspect that the drug was responsible in any way".

The CSM estimates that if 12 drugs were monitored simultaneously, a general practitioner might expect to receive six such questionnaires to complete in a year—the patients would not be directly approached to give information. The events recorded on the forms would then be analysed centrally. The aim would be to generate hypotheses—of safety as well as of toxicity—which could be tested by referring to the CSM's register of adverse reactions and to the scientific literature. This procedure would continue until 100 000 patients had received the drug, which in the case of a common one, might take about two years. If nothing serious had emerged by then, a smaller random sample of patients would be followed up to watch for any long-term effects. Record linkage has the same aim as RADS but differs from it mainly because it is based on hospital admissions and not on general medical practice. □

IN CONFIDENCE — REPORT ON SUSPECTED ADVERSE REACTIONS

1. Please report all reactions to recently introduced drugs and serious or unusual reactions to other drugs. (Vaccines, dental or surgical materials, IUCDs, absorbable sutures, contact lenses or associated fluids should be regarded as drugs).
2. Record on the top line the drug you suspect of causing the adverse reaction.
3. Record all other drugs, including self medication, taken in the previous 3 months. With congenital abnormalities, record all drugs taken during pregnancy.
4. Do not be deterred from reporting because some details are not known.
5. Please consider the possibility of interaction.

NAME OF PATIENT (To allow linkage with other reports for same patient. Also give record number for hospital patient)	SEX	AGE OR DATE OF BIRTH	WEIG

DRUGS* (Give brand name if known)	ROUTE	DAILY DOSE	DATE STARTED	DATE ENDED	INDICATIONS

*For Vaccines give Batch No

REACTIONS	STARTED	ENDED	OUTCOME (e.g. fatal, re

ADDITIONAL NOTES

REPORTING DOCTOR

Name

Address

Tel No 48

Signature

Date

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Is safety too expensive?

FOR THE first time since the Thalidomide tragedy twenty years ago, the regulations governing drug-testing in Britain are to be eased. The proposals, which have been made without public discussion or reference to Parliament, were described last week by Patrick Jenkin, Secretary of State for Social Services as "a watershed in drug regulations."

Concern has been expressed, however, that the new moves are being made, not for safety reasons, but because too strict regulations are apparently leading the pharmaceutical industry to conduct a growing number of clinical trials abroad.

The main changes, proposed by the Committee on Safety of Medicines, and due to be introduced shortly are:

- Only one species of animal need now be used in safety tests before human trials begin—provided the drug can be shown to work in humans in an "approximately similar way." Previously at least two species of animal were obligatory.
- Fertility studies, which can take up to nine months to complete, will no longer be required before clinical trials begin, provided women of child-bearing age are excluded.
- Human beings can now be subjected to a three-day period of testing in the course of toxicity studies, following a 14-day animal experiment. Up to now this period has been limited to one day.

The changes are not in themselves so radical as to ferment widespread anxiety about drug safety procedures, and there is some disagreement about how significant they are. But the secrecy in which they have been decided has given rise to concern, and they could well mark the beginning of more serious de-regulation.

The Association of Community Health Councils—the official watchdog for patients within the NHS—has expressed serious concern on a number of fronts. It argues that the changes offer no benefit to the patient; that they shift the risk-benefit equation for the patient to the risk side; and that the new regulations could encourage drug companies to use the UK as a testing ground for the development of all new drugs.

The CHCs are particularly worried that the interests of industry, rather than any great concern for patient benefit, seem to have been the motive force behind the changes.

In a letter circulated by the DHSS earlier this year, the department made it clear that keeping investment as well as expertise in Britain was the prime reason for rethinking current drug-testing procedures.

The letter explained that "The transfer abroad of clinical trials . . . would also adversely affect medical research as a whole in both the universities and the NHS, as well as industry itself." And in a special briefing for The Sunday Times last week the DHSS confirmed that the intention of the proposals is to encourage companies to perform more clinical trials in this country.

There are, however, other reasons for de-regulation according to Oxford University's Professor of Pharmacology, David Grahame-Smith, who chaired the key working party. He explains that "over the years the business of testing drugs prior to going to clinical trial has grown like Topsy. There is no pre-ordained truth about how to do it. Some tests, which are not giving any useful data are not required—they simply take up resources better put to finding new treatments."

But not everyone involved in drug testing agrees about which tests are indispensable. Frank Sullivan, a senior pharmacologist at Guy's Hospital, who sits on the Pesticides Committee and also advises the World Health Organisation, is particularly concerned that fertility trials ("reproductive toxicity testing") will no longer be required as long as women of child-bearing potential are excluded.

This means that under the proposed rule change it will be possible for all the clinical trials on perhaps hundreds of males to be completed without a single study to test for effects on male fertility and reproduction.

The DHSS for its part questions the value of such studies and says the change is simply bringing Britain into line with other drug-testing countries in Europe as well as America.

The CHCs feel that in the absence of wider public discussion, the assumptions on which the proposals are based have slipped by unexamined. Dr Rod Griffiths, chairman of the Association, questions whether it is necessary to increase the risks to patients by reducing pre-clinical testing, and is particularly concerned at the contradictions between the CSM's responsibility for the safety of drugs for patients and its role here: "What the hell have such proposals got to do with a Committee on the Safety of Medicines?"

Jill Rakusen and Elaine Potter

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Analgesics

Is the 50 year search finally over?

The result of a 10 year, multi-million pound research and development programme by McNeil Pharmaceutical US, is a new non-narcotic analgesic drug called Zomax (Zomepirac sodium). The drug, launched in the UK in March by Ortho Pharmaceutical, sister company of McNeil, has already received fairly wide publicity as the analgesic that has been proven more effective than aspirin and at least as effective as oral narcotics.

Zomax was approved for sale in the US last year and has achieved reasonable success. It is hoped that this will be followed by a similar reaction in the UK. Last month, a spokesman for Ortho said, 'the initial response to the launch of Zomax has been even more encouraging than projected. We anticipate that Zomax will become a widely used analgesic throughout the UK'.

The search for an analgesic that is orally effective for a wide range of pain, yet is non-addicting and well tolerated, has been going on in the US for 50 years. Dr Wendy Jefferson, medical director of Ortho said of Zomax that 'it fulfills these needs and represents an important advance towards effective and safe pain relief'.

Zomepirac (5-(4-chlorobenzoyl)-1,4-dimethylpyrrol-2-yl acetic acid) was first synthesised in 1969 by McNeil. It is thought to interrupt the pain impulses at the site of injury by inhibiting prostaglandin synthesis. Furthermore, Dr Stanley Gottlieb, director of clinical investigation at McNeil, believes that there is evidence to suggest 'that it is possible that Zomax ... may also reach sites in the spinal cord and/or brain'.

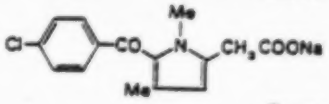
Studies of the effects of Zomax on humans began six years ago. This drug has been subjected to probably the most comprehensive study of an analgesic ever, since it involved 200 doctors and more than 7200 patients.

These tests were carried out using 100 mg doses of Zomax and comparisons were made with: aspirin 650 mg; dextropropoxyphene napsylate 100 mg with paracetamol 650 mg; two APC each with 30 mg of codeine phosphate; and oral pentazocine 50 mg. Zomax was found to be significantly more effective than aspirin and dextropropoxyphene with paracetamol and equally as effective as APC with codeine. In the treatment of post-operative pain, Zomax was at least as effective as pentazocine.

Its potency for the treatment of various types of pain was also studied and it was found to be effective for chronic muscle and joint pain, low back pain, dental pain, sprains, fractures and post-operative pain.

Zomax is non-addictive according to Ortho, since after 12 months' therapy, no withdrawl symptoms were observed and the most frequently reported side effects were gastrointestinal; the most common of these was nausea.

The cost to the National Health Service of 100 tablets of Zomax 100 mg is, at the time of going to press, £9.96. The prices listed in the *British national formulary 1981* for codeine and pentazocine give reasonable comparisons with Zomax since their cost to the NHS is within a similar price bracket. However, aspirin and Distalgesic (dextropropoxyphene with paracetamol) are listed as having relative prices of up to £1 per 100 aspirin and between £1.05 and £2.50 per 100 Distalgesic tablets. Zomax is available on prescription only.



Zomepirac sodium

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Professor K J Murton,
Dr D F Ball and
Dr H W Wardale

A market for pharmaceuticals?

This article describes a valuable exercise in industrial liaison and in the education of undergraduates on an interdisciplinary course in chemistry and business studies. It enabled the students to consider both technical and commercial constraints in formulating decisions on a future research and development programme.

The honours degree course in chemistry and business studies at Salford University is now in its third year. Two of the major course objectives are the linking of the business and chemical studies and the linking of the course itself with the process industries. The students undertake a number of activities in pursuit of these aims. The sandwich course element makes a particularly important contribution to this, but even during the time spent in the university special periods are set aside for developing links with industrial practice. This article presents a detailed description of a recent session with a group of nine students who had just completed the first year of the course. As this proved to be a particularly successful activity it is hoped that this report will not only exemplify the techno-commercial link but also provide teachers with a stimulus to develop this kind of seminar as part of school activities.

The seminar took the form of an extended decision-making simulation exercise with the students becoming the board of directors of an international company with the seminar leader (KJM) acting as the chairman of the board. Other staff members were present as observers but were made non-executive directors and allowed to comment when invited. The first morning session was relatively short. The chairman 'reminded' the board of the main features of the company's activities in recent years. Although the hypothetical company's major product area has always been pharmaceuticals the contribution of this sector of activity to both turnover and profits has been falling. At a previous and entirely imaginary meeting the board has already decided that in order to maintain profitable growth it is essential to improve the performance of the pharmaceutical sector and has agreed that about one million US dollars should be invested in new R & D in pharmaceuticals. The chairman now required the board to develop a detailed policy for the reinvigoration of the pharmaceutical sector. For the purposes of the exercise this was carried out in two main stages. The board was first asked to identify potential areas for new drugs and/or drug applications. Checklist 1 was given out to provide some assistance and the chairman, having requested that the full board should reconvene in about three hours to discuss their proposals, then withdrew leaving the student directors to tackle the problem.

Possible new areas

When the chairman rejoined the board in the afternoon session the directors reviewed their progress and suggested two possible major areas for the new R & D investment: a drug for the relief of menstrual pain and tension and a drug for the treatment of allergies. The chairman then led a detailed and extended discussion by posing a series of questions relating to these proposals in an attempt to establish criteria that would enable a selection to be made. Some idea of the scope of this discussion can be gained from the following list of questions.

- What is the backlog of existing ideas from which to start R & D?
- What is the strength of any existing competition?
- What are the symptoms which require alleviation?
- What is the duration and frequency of the symptoms?
- Is there a real need for the symptoms to be alleviated?
- In what dose form should it be marketed? What size of pack is required? How discreet would it need to be? Would it be different in different outlets (supermarkets, chemists).
- How much will the customer be prepared to pay? How will you ensure you get the right price in the first market?
- How will the product be advertised? Women's magazines, television, leaflets in chemists? Will different advertising be required for differing age groups?
- What medical advice is required? Will representatives need new training?
- What will the market surveys, questionnaires, *etc* cost?
- Will success embarrass the company?

Drug for the relief of menstrual pain and tension

- In each of the markets being considered (Europe, N. America and Australia) how many women are in the appropriate age group?
- What is the importance of the menstrual function? If the drug operates by eliminating menstruation will this be psychologically acceptable?
- Will there be any social pressure constraining the acceptability of such a drug?

Drug for the treatment of allergies

- What are the allergies which are potentially capable of treatment by an 'over the counter' drug?
- Do enough people suffer from the same allergy to make this development feasible?

Using hay fever as the base case

- How many suffer from it and how badly? What is the age range and distribution?
- What are the seasonal variations and in what areas does it occur?

Checklist 1

1. What will existing drugs do (*eg* relieve pain)?
2. What will existing drugs not do (*eg* new limbs grow after amputation, baldness cured)?
3. What do we want new drugs to do (*eg* a togetherness pill to reduce marital breakdown, a remembering drug, a drug to cure warts)? Make a substantial list.
4. Of the suggestions on the list, which would meet an existing need and which is for a need that would have to be demonstrated (*eg* tobacco would be an example of the latter type)?
5. What is the company objective in relation to new drugs (*eg* profit maximisation, establishment of a loss leader image with prestigious development)?
6. What are the intrinsic assumptions in relation to company objectives (*eg* that drugs can still be marketed under brand names)?
7. What are the companies' expectations of this new product (*eg* 10 year product cycle)?
8. What are the alternative courses of action?
9. If competitors pursue the same logic and enter the same area can we survive the competition (*eg* refuse incinerators in the UK)?
10. What is the decision we reach?
11. How do we set about implementation (*eg* is the time now right)?
12. What is the probable impact and its consequences (*eg* if it fails in a catastrophic way could it ruin the other activities of the company)?

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• What are disadvantages of existing products (*eg* drowsiness)
• What will be the dose form? Will it be a lozenge for instant relief which is sold over the counter or a course of treatment in advance or during the 'hay fever' season?

This discussion completed the first stage of the exercise and at the end of the afternoon the chairman set out the requirements of stage two. Bearing in mind the points raised and perhaps partly resolved in the discussion the student directors were required to make and justify a choice between the two proposals and then to construct an outline plan for implementing the decision. Checklist 2 was supplied to help at this stage.

The choice

The full board reconvened at about 10 am the next morning but it was clear that the student directors had already been in discussion for some time. The chairman was somewhat surprised to learn that by a majority decision the board had selected the drug for the relief of menstrual pain and tension as its major investment area. The main reasons given for this choice were that it was anticipated that this would be a single product having a steady demand and initially no competition. The ensuing discussion was concerned with the problems of implementing the proposed programme. Again a list of questions is the best way of illustrating the scope of the discussion.

• Is it possible to predict the type of molecular structure which would be needed? Would the final preparation be a single substance or an admixture of existing or new drugs?
• How would it be possible to test the drug for efficacy and side effects?
• Where would the R & D be located?

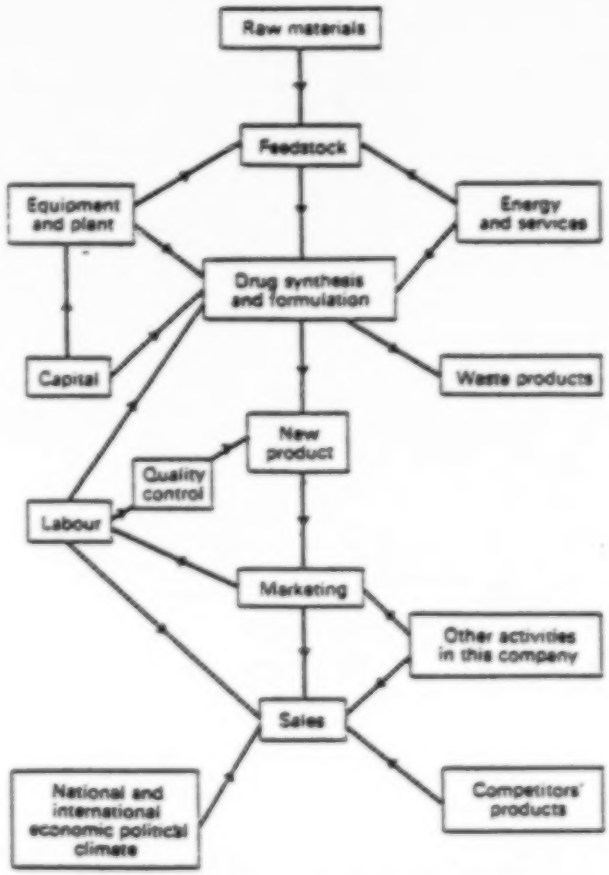
Assuming the successful completion of R & D

• What are the raw material requirements? What quality control will be needed? Can existing manufacturing equipment be used? If not, is there an existing plant which will do the job which can be acquired? If new plant is required where will it/they be located? (Consider taxation, government grants, tariff barriers in addition locational factors for a single country.) What is the optimum size and number of plants? What will be the cost of maintaining patent protection?
• What will be the dose size? Will it depend on body weight? How will it be packaged? Will it be in a handbag size suitable for one menstrual period only or in twin pack with sanitary towels? Can existing packaging machines be used? Could it be sold through existing vending machines? Is there the possibility of special health hazards for those involved in packing the drug over a long period of time?
• Where will the capital come from for the 'launch'? Where will the product be advertised? (TV, women's magazines, hairdressers?) Can existing retail outlets be used?
• Will it be possible to achieve long term contracts with retail chains? What trademark will be used and will it be linked to existing company trademarks?
• And finally where next?

In a concluding session the chairman reviewed the ground covered in the previous day and a half bringing into perspective the major points that had arisen and assessing and criticising the performance of the board. All those involved in this game agreed that they had gained some insight into industrial thought and a greater appreciation of the constraints operating upon business decisions and that it had been not only thought-provoking and academically worthwhile but also a thoroughly enjoyable exercise for both students and staff.

Professor K. J. Murton is Vice President, R & D with Nicholas International and visiting professor in the department of chemistry and applied chemistry at the University of Salford where Dr D. F. Ball and Dr H. W. Wardale are course tutors in chemistry and business studies.

Checklist 2



The diagram for checklist 2 is not intended to be complete but shows some of the factors that will influence production and sales of your new drug. It also indicates some of the interactions. You must think out the constraints that these factors and others have that have been left off the diagram and how their interactions would modify production of your new drug.

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PRODUCTION TEAM

Maisie Clubb
Kirsty Letton
Lorraine Logan
Alan Johnstone
Douglas McConnach

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